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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,543	04/09/2002	Satoru Yokomizo	12218/3	1045

23838 7590 02/08/2005

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

2/07/05 LA

Office Action Summary	Application No.	Applicant(s)	
	10/019,543	YOKOMIZO ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10,11 and 14-25* is/are rejected.

7)☒ Claim(s) *9,12 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/07/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response filed 11/08/2004. Claims 1-3 and 5-25 are pending and under consideration in this action. All objections/rejections not repeated herein are hereby withdrawn. Where applicable a response to Applicants' arguments will be included in the body of any objection/rejection repeated herein. As new grounds of rejection set forth, this action is nonfinal.

Priority

It is noted that Applicants suggest that the U.S. Patent and Trademark Office should contact the International Bureau to obtain certified copies of foreign patents on which Applicants are claiming priority. It is the Applicants' responsibility to ensure certified copies are submitted and failure to do so can be deemed as a waiver of any priority claim. See 35 U.S.C. 119(b).

Claim Objections

Claims 9-10 and 12-13 are objected to, because of the following informalities: The claims recite acronyms without first defining the corresponding definition. Furthermore, the specification does not provide a definition for the terms, "ALK1", "ALK3" or "XPR2".

This objection was made in the previous action and is maintained. Applicants assert that the terms stated above are "formal technical terms" representing genes encoding p450 enzymes (ALK1 and ALK3) or an alkaline extracellular protease (XPR2). The terms are not deemed terms of art that would be recognized as such by one of skill in the art. In fact, the terms can have multiple meanings in the art of biochemistry.

For example, the term "ALK1" is used as an acronym for "activin receptor-like kinase 1" which is distinguishable from the corresponding definition relative to instant application – "alkane-inducible cytochrome p450 gene". Irrespective, within the context of the instant application, the terms are monikers for specific genes, not formal technical terms. Appropriate correction is required.

The following are objections necessitated by amendments to the claims or addition of new claims: Claims 9-10 and 12-13 are objected to because the claims as amended recite that a promoter or terminator is isolated from a particular yeast species gene (i.e., genes ALK3, XPR2 and ALK1). However, as written, the acronyms ALK3, XPR2 and ALK1 are recited without any identification as a gene. The term "gene" should be inserted after the particular acronym wherever such acronyms occur in claims 9-13. Appropriate correction is required.

Claims 24 and 25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Base claim 1 already recites the genera of *Yarrowia* and *Candida* to which claims 24 and 25 are drawn respectively, thus it is unclear how said claims are further limiting.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 15-16 and 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

These are new grounds of rejection necessitated by amendment.

Claim 15 is directed to a transformant wherein the polyester synthesis-associated enzyme (PSA) gene comprises either a polyhdroxyalkanoate synthase (PHA) gene from *Aeromonas caviae* or PHA and a hydratase gene. Therefore, the claim as written is directed to the gene comprising either a PHA gene or a PHA and a hydratase gene, thus a single gene encodes two disparate enzymes (i.e., PHA and hydratase). Are Applicants suggesting that a single PSA gene actually comprises two genes, thus encodes two different proteins? Because of this ambiguity, the claims' metes and bounds are indeterminable.

Claim 18 is directed to a PSA gene where at least one CTG codon is replaced with substitute codons that encode leucine, and the claim recites the phrase "said gene functions in a yeast which translates the codon CTG into serine". As written the claim is discordant, as between "said gene" and "translates the codon CTG into serine". More particularly, "the codon CTG", pursuant to the claim language, refers to a CTG that has been modified. Therefore the claim reads on a CTG that is substituted with TTA, TTG, CTT, CTC or CTA codons encoding leucine, where said modified codon ("the codon CTG") is translated into serine. In other words, the phrase "the codon CTG" in fact delimits the modified CTG codon that is no longer a CTG codon. Therefore, as written, the claim is vague and indefinite making the claims' metes and bounds indeterminable.

In addition, as written claim 18 is vague and indefinite, because the term "functions" confers ambiguity as to whether the gene, with a codon being modified in at least one CTG, is now translated into serine in any yeast. In other words, because the term "functions" delimits the gene, the claim could be interpreted to mean that the modification of a CTG codon correlates to a yeast cell translating said modified codon into serine.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claim1-3, 7, 14-17 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukui et al. (US 5,981,257; the '257 patent; reference already of record).**

This rejection was made previously and is repeated herein. A response to Applicant's arguments is set forth immediately below. The claims, as amended, are directed to a transformant that comprises a PSA gene, a promoter and a terminator, where the transformant is delimited to several genera of yeast including *Candida*. The limitation, "terminator" is interpreted as broadly as reasonable to also include situations where the terminator is comprised within the gene being expressed. In addition, claim 16 is directed to PHA gene "represented" by SEQ ID NOs: 3 and enoyl-CoA hydratase gene "represented" by SEQ ID NO: 4, where the term "represented" is interpreted as broadly as reasonable to mean a gene comprising the sequence encoding the PHA synthetase or said hydratase of *Aeromonas caviae*.

The '257 patent teaches cells transformed with nucleic acids that comprise a polyester synthase gene wherein the polyester polymer formed comprises 3HB-co-3HH. (e.g. col. 1, ll. 25-55; col. 11, Table 3). Furthermore, the PHA gene or the enoyl-CoA hydratase gene that is obtained from *Aeromonas caviae*. (e.g., col. 3, l. 32; col. 7, ll. 20-66). The '257 patent explicitly teaches that the host organism, transformed with an expression vector, can be yeast, more particularly *Candida*. (e.g., col. 4, l. 26). Furthermore, if yeast are to be used as the host organisms, the '257 patent teaches that appropriate expression vectors, such as Yep13 or Ycp50 can be used to provide appropriate promoters/terminators, whereby an expression construct comprising a gene would necessarily comprise a promoter and terminator functional in the host yeast cell. (e.g. col. 4, l. 47). Therefore, the '257 patent anticipates the rejected claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that the '257 patent does not disclose a terminator as recited in claim 1, thus the reference does not anticipate the rejected claims. As stated above, a gene comprised on the expression vector/construct would necessarily contain a terminator codon (e.g., in the open reading frame), thus the '257 does teach this additional limitation. Applicant does not set forth any additional arguments with respect to the rejected claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. **Claims 1-3, 7, 14-15, 17 and 25 rejected under 35 U.S.C. 103(a) as being unpatentable over Leaf et al. (Microbiology, 1996; 142:1169-80; see whole document; reference already of record) and further in view of Fukui et al. (US 5,981,257; the '257 patent).**

The claims are interpreted consonant with the stated interpretations above. (Supra, Rejection No. 2). This reference was previously applied to the claims, which were directed broadly to any yeast transformant. Applicant's amendment of claim 1 introduces delimits yeast to particular genera, that are not explicitly taught by Leaf et al.

Leaf et al. teach expressing a bacterial polyhydroxybutyrae synthase in *Saccharomyces cerevisiae*. (e.g. Abstract; p. 1170, col. 2, under Plasmid Construction). More particularly, an expression cassette (pTL85) contains the necessary promoter/terminator elements for expression is *S. cerevisiae*. (e.g. p. 1170, col. 1, under "Methods"; col. 2, under "Plasmid Construction"; p. 1171, col. 2, last ¶ bridging to p. 1172). Furthermore, the expression construct, comprising a gene, would necessarily contain a terminator.

Leaf et al. do not disclose additional yeast species in which PHA genes can be expressed to produce polyesters. In addition, the reference does not teach that the PHA gene is from *A. caviae*, or the gene represented by SEQ ID NO: 3.

However, the '257 patent teaches that PHA genes from *A. caviae* will operate in the same yeast cells as Leaf et al. (i.e., *S. cerevisiae*). In addition, as stated previously, the '257 patent teaches that additional yeast, such as *Candida*, can be transformed with the PHA gene from *A. caviae*. (e.g., col. 4, l. 26). Both Leaf et al. and the '257 patent teach transformed yeast cells expressing PHA genes in order to harvest polyesters therefrom. Indeed, Applicant's own disclosure teaches that the yeast cells used are not particularly important. (e.g., Specification, p. 6, ll. 30-33). Furthermore, the '257 patent teaches that the host cells used are not particularly limiting. (e.g., col. 4, ll. 16-20).

Therefore, it would have been obvious to modify the variety of yeast cells and the PHA gene as taught by Leaf et al. with the yeast cells and PHA gene as taught by the '257 patent. One would have been motivated to use different combinations of PHA genes and yeast cells so as to optimize conditions for polyester production and to expand the range of culture/bioreactor systems that could be used to effect polyester production. Given the level of skill at the time of invention, there would have been a reasonable expectation of success to substitute the types of yeast cells or PHA gene as taught by Leaf et al. with the yeast cells and PHA gene as taught in the '257 patent.

4. **Claims 1-3, 5, 7-8, 10, 14-15, 17, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Fukui et al. (US 5,981,257), further in view of Park et al. (J. Biol. Chem. 1997; 272(11): 6876-81).**

Additional limitations further particularize the species of yeast to *Yarrowia lipolytica* and further particularize the promoter in the expression construct to a promoter of the XPR2 gene isolated from *Y. lipolytica.*

The '257 patent does not explicitly teach that *Y. lipolytica* can be the transformed yeast cell, but as stated previously, the reference explicitly states that the type of cell is not particularly limiting (e.g., col. 4, ll. 22-28), an assertion that is also disclosed in instant specification. (e.g., p. 6, bottom). In addition, the '257 patent does not teach that the promoter on the expression construct can be from the XPR2 gene isolated from *Y. lipolytica.* The '257 patent is drawn to the art of utilizing yeast cells, such as *S. cerevisiae* or *Candida* in expression of heterologous proteins (e.g., PHA enzymes).

Park et al. teach transformed cells wherein expression constructs containing XPR2 promoters/terminators are used in a system for expression of heterologous proteins in *Y. lipolytica.* (e.g., Abstract). More particularly, *Y. lipolytica* is transformed with expression constructs, with said XPR2 gene promoter/terminators, in order to express a heterologous α-Amylase enzyme. Therefore, the issue can be framed as whether one of skill would recognize that various yeast cells, particularly *Y. lipolytica*, could be utilized in expressing heterologous proteins/enzymes, such as PHA. Park et al. teach that *Y. lipolytica* provides certain advantages of *S. cerevisiae*, in a process of using transformed cells to express a heterologous protein. (e.g., p. 6876, col. 1, ¶ 1, bridging to col. 2, ¶¶ 1-2). Furthermore, Park et al. teach that it is well known in the art that the XPR2 gene comprises a strong promoter that has been used to express heterologous proteins in *Y. lipolytica.* (e.g., p. 6876, col. 2, ¶ 3).

Therefore it would have been obvious to substitute the transformed cells as taught by the '257 patent, with the transformed *Y. lipolytica* cells comprising the XPR2 promoter/terminator constructs as taught by Park et al. in order to obtain the benefit of a strong and well tested yeast cell system necessary to express a heterologous protein (e.g., PHA enzyme). One would have been motivated to make such a substitution to expand the range of yeast cell cultures that could be used to produce the heterologous proteins such as the PHA enzymes, as well as to obtain the benefits taught by Park et al. compared to *S. cerevisiae* as the culture cell. Given the level of skill at the time of invention, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the transformed *S. cerevisiae* cells of the '257 patent with the *Y. lipolytica* transformed cells as taught by Park et al.

5. **Claims 1-3, 6-7, 11, 14-15, 17 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Fukui et al. (US 5,981,257), further in view of Masuda et al. (Curr. Genet. 1994; 25:412-417) and Faber et al. (Yeast. 1995; 11:1331-1344).**

Additional claims delimit the genera of *Candida* to the species *C. maltosa*. Neither, Park et al. or the '257 patent explicitly recite *C. maltosa* as a species of yeast cells that can be transformed with expression constructs encoding the PHA gene. As stated above the '257 patent and Applicant's own disclosure teach that the particular yeast cells used are not limiting and the '257 patent explicitly states that yeast from the genus *Candida* can be used to produce heterologous PHA enzyme (Supra, Rejection No. 2).

The '257 patent does not teach using *C. maltosa* as transformed cell to express a heterologous protein such as PHA enzymes.

C. maltosa is an art recognized species of *Candida* that has been used to express heterologous proteins. For example, Masuda et al. teach expression of endogenous as well as heterologous genes in *C. maltosa*. More particularly, *C. maltosa* provides a useful cell system for expression of heterologous enzyme, especially where said enzyme can be contained within both the endoplasmic reticulum and peroxisome. (e.g., p. 412, col. 2, ¶ 3). In addition, Masuda et al. teach that promoter elements are obtained from *C. maltosa* in constructing the expression vector with which the cell is transformed. (e.g., p. 413, under Materials and methods).

Furthermore, Faber et al. teach that a methylotropic yeast such as *Candida* represent attractive substitute to other yeast cells, as transformants that produce heterologous proteins. (e.g., p. 1332). In addition, methylotropic yeasts represent ideal transformants because of their tightly regulated promoter elements. (e.g., p. 1334, col. 1, ¶ 3).

Therefore, it would have been obvious to one of ordinary skill in the art to use alternative methylotropic yeast such as *C. maltosa* as taught by Masuda et al. and Faber et al., in place of *S. cerevisiae* as taught by the '257 patent to produce transformants that express heterologous proteins such as the PHA enzyme of the '257 patent. One would have been motivated to do so to extend the range of different methylotrophic yeast cells that can be used to express heterologous genes (e.g., PHA gene from bacteria) and to obtain the benefit of tightly regulatable expression. Furthermore, given the level of skill in the art at the time of invention, there would have been a reasonable expectation of success to use alternative transformants to express PHA genes (i.e., heterologous protein expression). Therefore, the rejected claims are unpatentable over the '257 patent in view of Masuda et al. and Faber et al.

Allowable Subject Matter

Claims 9, 12 and 13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER